

Claims 16, 17 and 18, line 2, respectively, after "amount" insert --for eliciting cellular immune response--

Claims 19, 20 and 21, line 4, respectively, after "amount" insert --for eliciting cellular immune response--

Cancel Claim 3.

R E M A R K S

The pending claims have been amended so as to more accurately and precisely define the invention, particularly in the light of the Examiner's comments in the Office Action. Claim 1 has been amended to be directed to a peptide derived from protein E6 or E7 HPV 16 or HPV 18. Claims 16-21 have been amended to remove any ambiguity from these claims and to better define the invention. Complete support for the amendment to Claim 1 is to be readily found in the application as filed, see also particularly the originally submitted claims.

In the Office Action the Examiner noted that the Information Disclosure Statement filed January 4, 1994 failed to comply with 37 C.F.R. 1.98(a)(3) in that it did not include a concise explanation of the relevance to the subject invention and application. By a separate communication, applicants are forwarding the new substitute Information Disclosure Statement.

In the Office Action the Examiner objected to the specification and to the claims based on 35 U.S.C. 112, first paragraph, as not providing an adequate description of the invention and failing to teach how to make and/or to use the invention, i.e. failing to provide an enabling disclosure. The Examiner, however, noted that the disclosure is enabled with respect to nanopeptide sequences from E6 or E7 genes of HPV 16 OR HPV 18. The Examiner also noted that the reference Matlashewski et al discloses that HPV 18 may be diagnostically useful since these proteins have been identified in specific human cancers. The Examiner by way of further explanation noted that the methods claimed herein are not known in the art and the Examiner suggested an amendment to the claims to what is supported in the specification or by filing of evidence in the form of a Rule 132 Declaration supporting applicants' broad range.

The Examiner also noted that the disclosure should contain details so as to enable a person skilled in the art to make and use the invention. As an added comment, the Examiner mentioned that applicants' disclosure with respect to utility of applicants' claimed compounds, are "incredible" in the light of contemporary knowledge. The Examiner's suggested that evidence be submitted by applicants supporting the disclosure and claims. These objections to the specification were repeated with respect to the rejection of the claims.

In addition to objecting to the specification and the claims as lacking a supporting disclosure, the Examiner rejected the claims based on 35 U.S.C. 102(b) as anticipated by or, in the alternative, based on 35 U.S.C. 103 as obvious in view of Schoolnik et al. According to the Examiner, the claimed invention is drawn to a peptide from an HPV protein wherein the peptide binds to an MHC Class 1 molecule. The Examiner also noted that the claimed invention is also directed to a method of prophylactic or therapeutic treatment of HPV related diseases by administering a peptide from HPV proteins in a pharmaceutical composition.

With respect to Schoolnik et al., the Examiner mentioned that Schoolnik et al discloses synthetic peptides from HPV which are useful in the diagnosis and therapy of conditions associated with HPV infection. After briefly reviewing Schoolnik et al the Examiner stated that the teachings of Schoolnik et al anticipate applicants' claimed invention and, according to the Examiner, the compositions and methods disclosed by Schoolnik et al inherently possess properties which anticipate applicants' claimed invention or would make applicants' claimed invention obvious. The Examiner, however, indicated that applicants' should show a novel or unobvious difference between the claimed invention over the prior art.

Applicants' have carefully considered the disclosures of the prior art and the references cited and the Examiner's indicated

basis for the rejection of claims thereon. Applicants, however, respectfully submit that nowhere have applicants been able to find any teaching or suggestion of applicants' invention in the references cited. It is respectfully requested that the Examiner reconsider and withdraw the indicated basis for rejection of claims on the cited references.

Additionally, applicants herein point out how applicants' claimed invention is amply supported in the specification and how applicants' claimed invention patentably distinguishes over the references cited. For example, with respect to applicants' amendment to Claim 1 limiting Claim 1 to amino acid sequences derived from the proteins E6 or E7 of HPV 16 or HPV 18, it is mentioned that the specification and claims are enabled for more than just nonapeptides, see the nonapeptide listings in Claims 5 and 6. For example, where two overlapping nonapeptides from a total sequence of 10 amino acids, such as, for example, in the case of the two nonapeptides 11-19 of HPV 16 E7 and 12-20 of HPV 16 E7. Together, these follow the peptide-MHC binding rules described, for example, in Ruppert et al Cell, 1993, 74:929, and the references mentioned therein and wherein so-called anchor residues are disclosed. It is submitted that those skilled in the art would immediately see and realize that, for instance, 10 mers and also 11 and 12 mers would be included. Larger or longer peptides, such as a 10 mer peptide, is also specifically described in Kast et al J. Immunol., 1994, 152:3904. Moreover, those skilled in the art would

immediately discern that ~~a 3~~^{an 8} mer peptide, the common part of two overlapping 9 mer peptides, as in the case of peptides 85-93 of HPV 16 E7 AND 86-94 of HPV 16 E7, where the common part is the amino acid sequence or positions 86-93, would also be included in the claimed invention. That such peptide is indeed feasible is indicated in Kast et al, *supra*.

Concerning adequacy of the disclosure of applicants' invention with respect to prophylactic or therapeutic treatments by administering the peptide, it is pointed out that the basic principle for such treatments for HPV 16 related disease has been demonstrated, such as in mice, by Feltkamp et al J. Immunol. 1993, 23:2242. It is mentioned, however, that to demonstrate in humans that such a treatment would be beneficial would be unethical, as discussed by workers in the field and other leaders, see Science 1994, 266:537.

Concerning the Examiner's reference to Matlashewski et al, applicants point out that applicants' invention and claims are not related to the protein of HPV 18 E6 nor to the antibodies against fusion proteins and to the 14 mer peptide 2-15 of HPV 16 E6 to which an antibody reaction has been identified. Indeed the claims do not include that particular peptide since applicants' invention is directed to peptides that bind in the groove on top of an MHC Class I molecule. One skilled in the art, for example, would immediately realize that the Matlashewski et al peptide is too

long, and does not have the correct anchors for binding to an MHC class I molecule. Also, the reverse is true; if applicants would generate antibodies against free peptides, these antibodies would not be useful since they would not bind to the peptides once they are bound in the groove of an MHC Class I molecule. Accordingly, one skilled in the art would realize the fundamental difference between B cell epitopes (to which antibody responses are directed) and CTL epitopes

Further, applicants submit that their teaching on how to use the peptides is adequate and complete, since applicants have demonstrated how one could use such peptides in animal models, see Kast et al PNAS 1991, 88:2283. Thus, one skilled in the art would immediately know how to utilize applicants' peptides for the treatment and prevention of human diseases, such as, for instance, dissolving the peptides in an adjuvant and administering the mixture.

The Examiners' allegation is that applicants' disclosure and claimed utility borders on the incredible is questioned and it is respectfully requested that it be withdrawn. It is submitted that this objection tends to suggest that the Examiner is not thoroughly familiar with the pertinent literature. For example, in Kast et al Immunol. Letters 1991, 30:229, it is indicated that a peptide based approach of vaccination is feasible. That this has not yet been proven in humans, as indicated, is a matter of time since presently

it is unethical to use humans as guinea pigs. However, together with the U.S. company which owns the exclusive rights, when applicants' patent issues, applicants are obtaining approval from a medical-ethical committee for peptide-based clinical trials for HPV 16 related cervical cancer. Therefore, it is submitted that applicants' invention does not border on the incredible but actually is a clinical reality.

Further, supporting applicants' position are the articles of Ressing et al which show that peptide based vaccines work in human HLA transgenic mice and in "in vitro" immunization procedures. Also, the article of Vitiello et al J. of Clinical Invest. in press, deals with a peptide-based vaccine tested in a Phase I Trial to treat HBV related disease.

Concerning the Examiner's mention of the alleged absence of working examples and predictability of the *in vivo* efficacy of applicants' invention (i.e. applicants' peptides) the Examiner is requested to reconsider and withdraw the Examiner's position in the light of applicants' remarks herein and further consideration and evaluation of applicants' disclosure.

It is submitted that one skilled in the art would readily understand from the published literature, the mice studies of Kast et al PNAS 1991, 88:2283 and Kast et al Eur. J. Immunol. 1993, 23-1189, wherein between 1 and 100 µg of peptide were used for a mouse

of about 25 grams, how to determine the effective dose in humans based on solubility of the peptides in solution, such as dose in the order of also 1 μ g to about 3 mg. The precise dose for an individual, as is known, depends on weight, severity of the disease, adjuvant used, etc. and any simple dose escalation could readily be performed by one skilled in the art and, it is mentioned, is also part of the clinical trial for HPV 16 related cervical cancer, referred to hereinabove.

Concerning the Examiner's position that Schoolnik et al anticipates the claimed invention by disclosing peptides from an HPV protein wherein the peptide binds to an MHC Class I molecule, it is submitted that the Examiner's indicated position is unwarranted and unjustified based on the disclosures of Schoolnik et al. The Examiner, it is submitted, errs in the understanding of Schoolnik et al. In no way has Schoolnik et al shown or disclosed that their peptides bind to MHC class I molecules and are cytotoxic T lymphocyte epitopes. In fact none of the epitopes disclosed by Schoolnik et al is the same as applicant's claimed peptides. Schoolnik et al have disclosed epitopes which would induce antibody (B cell) responses and not CTL responses, applicants' invention. Applicants' peptides have to fit snugly in the groove of HLA Class I molecules. Antibodies against applicants' peptides would not be able to bind to the peptides once they are buried in the groove.

All of applicants' peptides are related to one particular HLA allele and can only be used for those who carry that HLA allele. The Schoolnik et al peptides, in contrast, are not related to HLA class I molecules because they are B cell epitopes. Of Schoolnik et al claimed seventeen peptides, only eight are related to HPV 16 E6 or E7. Three of these eight peptides (peptides 2-4) are clearly too long to bind into the groove of an HLA class I molecule which one skilled in the art knows will bind peptides of 8-12 amino acids.

The other prerequisite for a peptide to bind in the groove of an HLA Class I molecule is the presence of two anchor amino acid residues in the peptide that bind into pockets in the groove of the HLA molecules.

These anchors are located at position 2 or 3 and at the C-terminal position (either position 8, 9, 10, 11 or 12 depending on the length). A disclosure or summary of these anchor positions is indicated in Kast et al J. Immunol. 1994;152:3904. Peptide number 1 of Schoolnik et al does contain an anchor residue for HLA-A 0201 at the C-terminal end, namely an L. However there is no anchor for that HLA molecule present on position 2. Therefore, this peptide will not bind to this residue for HLA-A 0301 at the C-terminal end, namely an R anchor. However, there is no anchor for that HLA molecule present on position 2. Therefore, this peptide will not bind to HLA-A 0301.

Peptide number 6 of Schoolnik et al has a tolerated anchor at the C-terminal end for HLA-A 0201 but lacks a proper anchor at position 2. Therefore, this peptide also will not bind to HLA-A 0201.

Peptide number 7 of Schoolnik et al has a tolerated anchor for HLA-A 0201, namely an M on the C-terminal end and a tolerated anchor on position 2 for the same HLA-A 0201 molecule (T). In fact, this 9 mer was already tested by applicants, as indicated, in Figure 1 herein. It is the fourth blip from the left in Fig. 1. As shown, this peptide does not bind at all to HLA-A 0201. This is completely logical because Ruppert et al Cell 1993, 74:929 has indicated that peptides binding to HLA-A 0201 are not allowed to have D at position 1 and Schoolnik et al peptide number 7 has such a D.

Finally, the Schoolnik et al peptide number 8 does not carry a C terminal anchor residue for any of the HLA alleles and therefore also this peptide will also not bind to HLA molecules.

In summary, of the eight Schoolnik et al peptides, one was demonstrated by applicants not to have the binding ability to HLA molecules which is a prerequisite to be a CTL epitope and the other seven are not applicable to applicants' claimed invention. One skilled in the art can readily see that the peptides of Schoolnik et al do not have the correct length or the correct and necessary

anchor residues.

Therefore, in view of the foregoing remarks, entry of this amendment, reconsideration of the rejection of the claims on the references cited, favorable consideration of the newly amended claims and allowance of all the pending claims are earnestly solicited.

Respectfully submitted,

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paper is being deposited this
date with the U.S. Postal
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